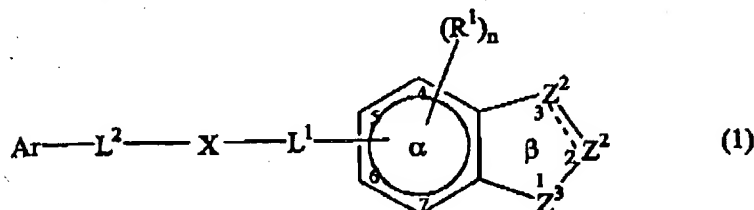


Application No.: 09/989,991

Docket No.: 219002029100

CLAIM AMENDMENTS

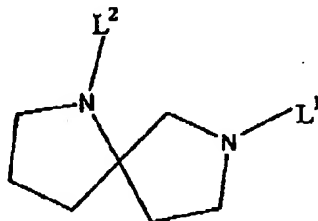
1. (currently amended) A compound of the formula:



and the pharmaceutically acceptable salts thereof wherein:

Ar is an aryl group substituted with 0-5 ~~non-interfering~~ substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR₂, SR, SOR, SO₂R, OCOR, NRCOR, NRCONR₂, NRCOOR, OCONR₂, RCO, COOR, alkyl-OOR, SO₃R, CONR₂, SO₂NR₂, NRSO₂NR₂, CN, CF₃, R₃Si, and NO₂, wherein each R is independently H, alkyl, alkenyl or aryl or ~~heteroforms thereof~~, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members;

L²-X-L¹ is of the formula:



L¹ is CO, SO₂ or alkylene (1-4C);

L² is alkylene (1-4C) or alkenylene (2-4C) optionally substituted with one or two moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, NH-aroyl, halo, OR, NR₂, SR, SOR, SO₂R, OCOR, NRCOR, NRCONR₂, NRCOOR, OCONR₂, RCO, COOR, alkyl-OOCR, SO₃R, CONR₂, SO₂NR₂, NRSO₂NR₂, CN, CF₃, and R₃Si, wherein each R is independently H, alkyl, alkenyl or aryl or ~~forms thereof containing 1-2 O, S and/or N atoms~~, and wherein two substituents on L² can be joined to form a non-aromatic saturated or unsaturated

sd-229672

Application No.: 09/989,991

Docket No.: 219002029100

ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety;

n is 0-3;

each R^1 is independently halo, alkyl, heteroalkyl, OCOR, OR, NRCOR, SR, or NR_2 ,

wherein R is hydrogen, alkyl, or aryl, or forms thereof containing 1-2 O, S and/or N;

 represents a single or double bond;

one Z^2 is CA or CR^2A ; the other Z^2 is CR^3 , CR^3_2 , NR^4 or N; and each R^2 , R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2 , SR, SOR, SO_2R , OCOR, NRCOR, $NRCONR_2$, $NRCOOR$, $OCONR_2$, RCO, COOR, alkyl-COR, SO_3R , $CONR_2$, SO_2NR_2 , $NRSO_2NR_2$, CN, CF_3 , R_3Si , and NO_2 , wherein each R is independently H, alkyl, alkenyl or aryl or forms thereof containing 1-2 O, S and/or N and two of R^2 and/or R^3 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^2 and/or R^3 is =O or an oxime, oximeether, oximeester or ketal thereof;

Z^3 is NR^5 or O; where R^5 is H or is optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR, SO_2R , RCO, COOR, alkyl-COR, SO_3R , $CONR_2$, SO_2NR_2 , CN, CF_3 , NR_2 , OR, alkyl-SR, alkyl-SOR, alkyl- SO_2R , alkyl-OCOR, alkyl-COOR, alkyl-CN, alkyl- $CONR_2$, or R_3Si , wherein each R is independently H, alkyl, alkenyl or aryl or forms thereof containing 1-2 O, S and/or N;

A is $-W_i-COX_jY$, where Y is COR^6 or an isostere thereof, each of W and X is substituted or unsubstituted alkylene or alkenylene, each of 2-6Å; each of i and j is independently 0 or 1; and R^6 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, SOR, SO_2R , SO_2NR_2 , OR, NR_2 , OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or forms thereof containing 1-2 O, S and/or N, or

sd-229672

3

Application No.: 09/989,991

Docket No.: 219002029100

wherein R^6 is OR, NR_2 , SR, $NRCONR_2$, $OCOR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl ~~or the heteroatom-containing forms thereof~~; and wherein two R attached to the same atom may form a 3-8 member carbocyclic or heterocyclic ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, ~~heteroalkyl~~, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2 , OCOR, $NRCOR$, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCOR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl ~~or forms thereof containing 1-2 O, S and/or N~~ wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined.

2. (canceled)

2 3. (original) The compound of claim 1 wherein Y is ~~an isostere of~~ COR^6 .

3 4. (original) The compound of claim 3 wherein Y is tetrazole; 1,2,3-triazole; 1,2,4-triazole; or imidazole.

4 5. (original) The compound of claim 1 wherein each of i and j is 0.

5 6. (previously presented) The compound of claim 1 wherein j is 0.

6 7. (original) The compound of claim 1 wherein Z^3 is NR^5 .

8. (canceled)

7 9. (previously presented) The compound of claim 1 wherein R^5 is H, or is optionally substituted alkyl or acyl.

10-11. (canceled)

8 12. (previously presented) The compound of claim 1 wherein R^2 and R^3 are independently selected from halo, OR and alkyl.

ad-229672

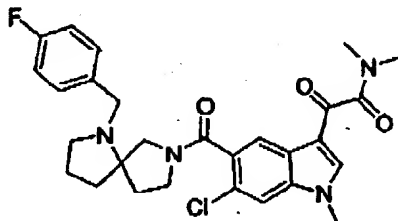
4

Application No.: 09/989,991

Docket No.: 219002029100

13-38. (canceled)

9 39. (previously presented) The compound of claim 1 wherein the compound is:



10 40. (currently amended) The compound of claim 1 wherein L^1 is CH_2 or CO and L^2 are independently selected from CO , $CHOH$, CH_2NHCO , CH_2NCH_3 , and CH_2 or $CHOH$.

11 41. (currently amended) The compound of claim 40 wherein L^1 and/or L^2 is CO .

42-44. (canceled)

12 45. (previously presented) The compound of claim 1 wherein L^2 and/or L^1 is unsubstituted alkylene.

13 46. (previously presented) The compound of claim 1 wherein L^2 and/or L^1 is unsubstituted methylene, or methylene substituted with alkyl.

47. (canceled)

14 48. (previously presented) The compound of claim 1 wherein Ar is optionally substituted phenyl.

15 49. (original) The compound of claim 48 wherein said optional substitution is by halo, OR, or alkyl.

Application No.: 09/989,991

Docket No.: 219002029100

16 50. (original) The compound of claim 49 wherein said phenyl is unsubstituted or has a single substituent.

51. (canceled)

17 52. (previously presented) The compound of claim 1 wherein R^1 is halo or alkoxy.

18 53. (original) The compound of claim 52 wherein n is 0, 1 or 2.

19 54. (original) The compound of claim 1 wherein L^1 is coupled to the α ring at the 4-, 5- or 6-position.

20 55. (original) The compound of claim 1 wherein Z^2 at position 3 is CA or CHA.

21 56. (original) The compound of claim 55 wherein the Z^2 at position 2 is CR^3 or CR^3_2 .

22 57. (currently amended) The compound of claim 56 wherein R^3 is hydrogen, or is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2 , SR, SOR, SO_2R , OCOR, NRCOR, $NRCONR_2$, $NRCOOR$, $CONR_2$, RCO, COOR, alkyl- $OOOR$, SO_3R , $CONR_2$, SO_2NR_2 , $NRSO_2NR_2$, CN, CF_3 , R_3Si , and NO_2 , wherein each R is independently H, alkyl, alkenyl or aryl or forms thereof containing 1-2 O, S and/or N and two of R^1 can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

23 58. (currently amended) The compound of claim 57 wherein each R^3 is selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl, heteroalkyl, heteroaryl, halo, OR, NR_2 , SR, NRCOR, alkyl- $OOOR$, RCO, COOR, and CN, wherein each R is independently H, alkyl or aryl or forms thereof containing 1-2 O, S and/or N.

24 59. (original) The compound of claim 55 wherein Z^2 at position 2 is N or NR^4 .

sd-229672

6

Application No.: 09/989,991

Docket No.: 219002029100

25 60. (currently amended) The compound of claim 59²⁴ wherein R⁴ is H, or alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, ~~heteroalkyl, heteroalkenyl, heteroalkynyl,~~ heteroalkylaryl, or is SOR, SO₂R, RCO, COOR, alkyl-COR, SO₂R, CONR₂, SO₂NR₂, CN, CF₃, or R₃Si wherein each R is independently H, alkyl, alkenyl or aryl ~~or forms thereof containing 1-2 O, S and/or N.~~

26 61. (currently amended) The compound of claim 1 wherein ~~—~~ represents a double bond.

62. (canceled)

27 63. (currently amended) A pharmaceutical composition ~~for treating conditions~~ characterized by enhanced p38 ~~α~~ activity which composition comprises ~~a therapeutically~~ ^{a therapeutically} effective amount of a compound of claim 1 and a pharmaceutically acceptable excipient.

64-67. (canceled)

28 68. (currently amended) ~~[[The]] A method to treat of claim 67 wherein said~~ proinflammation response is multiple sclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, septic shock, endotoxemic shock, Gram-negative sepsis, toxic shock syndrome, asthma, adult respiratory distress syndrome, stroke, reperfusion injury, CNS injury, psoriasis, restenosis, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft-versus-host reaction, Crohn's Disease, ulcerative colitis, Alzheimer's or pyresis which comprises administering to a subject in need of such treatment a compound of claim 1 or a pharmaceutical composition thereof

sd-229672

7